Itraconazole

Brand Name: Sporanox

Drug Description

Itraconazole, a synthetic triazole derivative, is an azole antifungal agent. [1]

HIV/AIDS-Related Uses

Itraconazole was approved by the FDA on September 11, 1992 for use in the treatment of adults coinfected with Penicillium marneffei infection and HIV. It is also approved for use as an alternative agent for the treatment or suppressive maintenance of cryptococcal meningitis in patients with AIDS and other immunocompromised conditions.[2] Itraconazole is also used orally for the prevention of serious fungal infections (e.g., coccidiodomycosis, cryptococcosis, histoplasmosis, mucocutaneous candidiasis) in patients with HIV infection.[3]

Non-HIV/AIDS-Related Uses

Itraconazole is indicated in the treatment of aspergillosis (especially in patients who are intolerant of or who are refractory to amphotericin B therapy); bastomycosis; oropharyngeal, chronic mucocutaneous, and vulvovaginal candidiasis; chromomycosis; coccidiodomycosis; histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; cryptococcal meningitis; onychomycosis; paracoccidiodomycosis; tinea corporis, tinea cruris, tinea pedis, and tinea manuum; extrameningeal cryptococcosis; cutaneous leishmaniasis; febrile neutropenia; fungal paronychia; Penicillium marneffei infection; fungal pneumonia; fungal septicemia; and disseminated sporotrichosis.[4]

Pharmacology

Itraconazole is fungistatic and may be fungicidal, depending on the concentration. Azole antifungals interfere with cytochrome P450 enzyme activity necessary for the demethylation of 14-alpha-methyl sterols to ergosterol, the principal sterol in fungal cell membranes. As ergosterol is depleted, the cell membrane is damaged. In Candida albicans, azole antifungals inhibit transformation of blastospores into the invasive mycelial form. Itraconazole, unlike ketoconazole, has a very weak, noncompetitive inhibitory effect on the cytochrome P450 enzyme system, while maintaining a high affinity for fungal cytochrome P450 enzyme activity. It has not been reported to have antiandrogenic activity, and does not affect cortisol metabolism with clinically recommended doses.[5]

Itraconazole requires an acidic environment for optimum absorption.[6] Gastrointestinal absorption of itraconazole is therefore affected by achlorhydria or hypochlorhydria (no or low acid levels in the stomach); because HIV infected individuals with these conditions have been reported, physicians should consider this in their decision to use itraconazole.[7] Itraconazole capsules should be taken with a full meal to ensure maximal absorption of the medication; itraconazole oral solution should be taken on an empty stomach to increase absorption of the medication.[8] Bioavailability of itraconazole when given in capsule form is 40% to 45% in the fasting state and 90% to 100% when taken with food; the bioavailability of the oral solution form is 90% to 100% in the fasting state and 55% when taken with food. The time to peak serum concentration may be from 2.5 hours to 4.4 hours, depending on formulation and whether or not the drug was taken with food.[9]

Itraconazole is highly lipophilic and is found extensively distributed to tissues, concentrating in fatty tissues, omentum (lining of the bowel wall), liver, and kidneys. Aqueous fluids, such as the cerebrospinal fluid, aqueous humor, and saliva, contain negligible concentrations of itraconazole. Itraconazole does not distribute into peritoneal dialysate effluent. Exudates, such as pus, may have up to 3.5 times the simultaneous plasma concentration of the drug, while tissues that are prone to fungal invasion, such as the skin, lung tissue, and the female genital tract, have several times the plasma concentration.[10]

Itraconazole is in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. Based on the teratogenic and embyrotoxic effects shown in animal studies, itraconazole should only be used during pregnancy

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Pharmacology (cont.)

or during nursing when the potential benefits justify the possible risks to the fetus or nursing infant. (4) Animal studies indicate that itraconazole causes a dose-related increase in maternal toxicity, embryotoxicity, and teratogencity. In rats, these consist of major skeletal defects at doses approximately 5 to 20 times the maximum recommended human dose (MRHD); in mice, these consist of encephaloceles and/or macroglossia at doses 10 times the MRHD. Itraconazole did not affect the fertility of male or females rats treated with oral doses of up to 5 times the MRHD, although parental toxicity was present at this dosage level. Itraconazole is distributed into breast milk.[11] [12]

Itraconazole binding to proteins is very high (99%). Metabolism of itraconazole is primarily hepatic. Biliary excretion of the capsule form is estimated to be 3% to 18%.[13] Adjustment of oral itraconazole dosage in patients with renal impairment appears to be unnecessary, but itraconazole injection should not be given to patients with creatinine clearances less than 30 ml/minute because severe renal impairment reduces clearance of hydroxypropyl beta-cyclodextrin (an excipient contained in itraconazole injection). While the effect of hepatic impairment on itraconazole pharmacokinetics currently remains unclear, plasma concentrations of the drug should be monitored carefully in patients with such impairment.[14]

Adverse Events/Toxicity

Adverse effects seen with azole antifungals include hypersensitivity; agranulocytosis; exfoliative skin disorders, including Stevens-Johnson syndrome; hepatotoxicity; thrombocytopenia; central nervous system effects; and gastrointestinal disturbances.[15]

The most common adverse events to itraconazole injection in pharmacological testing have been nausea, hypokalemia, bilirubinemia, diarrhea, and vomiting. The injection is associated with increased levels of hepatic enzymes, abnormal hepatic function, and jaundice, which may be indicative of possible liver disease. If patients develop clinical signs and symptoms consistent with liver disease, the administration of intravenous itraconazole should be discontinued. The oral solution is safe and generally well tolerated; the most common adverse effects are nausea, diarrhea, and fever.[16] The most common side effects seen with itraconazole capsule use in the treatment of systemic fungal infections have been nausea and skin rash.[17]

Drug and Food Interactions

In addition to those drugs contraindicated with its use, there are many drugs that may produce interactions if administered concurrently with itraconazole. Antacids, anticholinergics, antispasmodics, histamine H2-receptor antagonists, omeprazole, and sucralfate may increase gastrointestinal pH, reducing absorption of itraconazole. Patients should be advised to take these medications at least 2 hours after taking itraconazole. Concurrent administration of itraconazole with buffered didanosine should be carried out at least 2 hours before or 2 hours after didanosine is taken.[18] Patients with achlorhydria or hypochlorhydria (no or low acid levels in the stomach) will have decreased absorption of itraconazole. Itraconazole capsules should be taken with a full meal to ensure maximal absorption of the medication; itraconazole oral solution should be taken on an empty stomach to increase absorption of the medication.[19]

Concurrent use of itraconazole with oral antidiabetic agents, such as tolbutamide, chlorpropamide, glyburide, or glipizide, has increased the plasma concentrations of these sulfonylurea agents; hypoglycemia has been noted and blood glucose concentrations should be monitored, as the dose of oral hypoglycemia agent may need to be reduced. Itraconazole may inhibit the metabolism of the antineoplastics busulfan, docetaxel, and vinca alkaloids. Use of itraconazole with calcium channel blockers (e.g., felodipine, nifedipine, and verapamil) may result in edema; dosage adjustment may be needed. Caution should be used as itraconazole may inhibit calcium channel blockers' metabolism and these drugs can have a negative inotropic effect that may be additive to those of itraconazole.[20] [21]

Anticonvulsants (e.g., carbamazepine,

Drug and Food Interactions (cont.)

phenobarbital, and phenytoin) may decrease itraconazole plasma concentrations, leading to treatment failure or clinical relapse. Use of immunosuppressive drugs such as cyclosporine, methylprednisolone, sirolimus, and tacrolimus with concurrent itraconazole should be monitored carefully because itraconazole may inhibit their metabolism, increasing the plasma concentration of these drugs to toxic levels. Itraconazole may increase serum digoxin or alfentanil concentrations, leading to toxicity. Rifampin and rifabutin may increase the metabolism of itraconazole and other azoles, lowering the plasma concentration, which may lead to clinical failure or relapse. Macrolide antibiotics (e.g., clarithromycin and erythromycin) are known inhibitors of CYP34A and may increase plasma concentrations of itraconazole. The anticoagulant effects of warfarin may be increased when warfarin is used concurrently with any azole antifungal, resulting in an increase of prothrombin time; patients on such a regimen should be monitored carefully.[22] [23]

Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes, such as amphotericin B. Itraconazole may increase plasma concentrations of protease inhibitors (e.g., indinavir, ritonavir, and saquinavir); conversely, indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Nevirapine (and potentially other nucleoside reverse transcriptase inhibitors) may induce the metabolism of itraconazole, and has been shown to reduce the bioavailability of ketoconazole, another azole.[24]

Contraindications

Itraconazole is contraindicated for patients who have shown hypersensitivity to itraconazole and should be prescribed with caution to patients with hypersensitivity to other azoles. It should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy. Concurrent use of itraconazole with drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs; these include cisapride; oral midazolam, triazolam, and other benzodiazepines; pimozide; quinidine, dofetilide, and other antiarrhythmics that increase the QT interval; astemizole; and terfenadine. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as atorvastatin, cerivastatin, lovastatin, and simvastatin, are also contraindicated with itraconazole.[25] [26] [27] [28]

Clinical Trials

For information on clinical trials that involve Itraconazole, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Itraconazole AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (capsule and liquid), intravenous.[29]

Dosage Form: Itraconazole capsules, 100 mg.[30]

Itraconazole oral solution, 10 mg/ml.[31]

Itraconazole injection for intravenous infusion, 25 ml vials containing 10 mg/ml itraconazole in pyrogen-free solution.[32]

Storage: Itraconazole should be stored at below 25 C (77 F) and protected from light and freezing.[33]

Chemistry

CAS Name: 3H-1,2,4-Triazol-3-one, 4-(4-(4-(4-((2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-1-piperazinyl)phenyl)-2,4-dihydro-2-(1-methylpropyl)-[34]

CAS Number: 84625-61-6[35]

Molecular formula: C35-H38-Cl2-N8-O4[36]

C59.57%, H5.43%, Cl10.05%, N15.88%, O9.07%[37]

Molecular weight: 705.65[38]

Melting point: 166.2 C[39]

Physical Description: Itraconazole is a white to

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Chemistry (cont.)

slightly yellowish powder.[40]

Stability: After reconstitution with 0.9% sodium chloride injection, itraconazole for injection may be stored refrigerated (2 C to 8 C) or at room temperature (15 C to 25 C) for up to 48 hours, when protected from direct light. During administration, exposure to normal room light is acceptable.[41]

Correct preparation and administration of itraconazole injection are necessary to ensure maximal efficacy and safety. A precise mixing ratio is required in order to obtain a stable admixture. It is critical to maintain a 3.33 mg/ml itraconazole:diluent ratio. Failure to maintain this concentration will lead to the formation of a precipitate.[42]

Solubility: Itraconazole is lipophilic and practically insoluble in water and diluted acidic solutions.[43]

Other Names

Itraconazol[44]

Further Reading

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Manufacturer Information

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Sporanox
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430 Rt. 22 East
Bridgewater, NJ 08807-0914
(800) 682-6532

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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